

Applicant : Virginia W. Cornish
Serial No.: 10/705,644
Filed : November 10, 2003
Page 2

In the Claims

Please replace all prior versions of the claims pursuant to 37 C.F.R. §1.121 as modified by 68 Fed. Reg. 38611 (June 30, 2003) as indicated below.

1-132. (canceled)

133. (Original) A method for identifying a molecule that binds a known target in a cell from a pool of candidate molecules, comprising:

(a) covalently bonding each molecule in the pool of candidate molecules to a methotrexate moiety or an analog of methotrexate to form a screening molecule;

(b) introducing the screening molecule into a cell which expresses a first fusion protein comprising a binding domain capable of binding methotrexate, a second fusion protein comprising the known target, and a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein;

(c) permitting the screening molecule to bind to the first fusion protein and to the second fusion protein so as to activate the expression of the reporter gene;

(d) selecting which cell expresses the reporter gene; and

(e) identifying the small molecule that binds the known target.

134. (Canceled)

135. (Original) The method of claim 133, wherein the first or the second fusion protein comprises a transcription module selected from the group consisting of a DNA binding protein and a transcriptional activator.

Applicant : Virginia W. Cornish
Serial No.: 10/705,644
Filed : November 10, 2003
Page 3

136. (Original) The method of claim 133, wherein the molecule is obtained from a combinatorial library.

137. (Original) The method of claim 133, wherein the steps (b)-(e) of the method are iteratively repeated in the presence of a preparation of random small molecules for competitive binding with the hybrid ligand so as to identify a molecule capable of competitively binding the known target.

138-140. (cancelled)

141. (Original) The method of claim 133, wherein the first fusion protein or the second fusion protein is DHFR-(DNA-binding domain).

142. (Original) The method of claim 133, wherein the first fusion protein or the second fusion protein is DHFR-LexA.

143. (Original) The method of claim 133, wherein the first fusion protein or the second fusion protein is DHFR-(transcription activation domain).

144. (Original) The method of claim 133, wherein the first fusion protein or the second fusion protein is DHFR-B42.

145. (Original) The method of claim 133, where the cell is a yeast cell, a bacteria cell or a mammalian cell.

146. (Original) The method of claim 133, where the cell is *S. cerevisiae* or *E. coli*.

147. (Original) A method for identifying a molecule that binds a known target in a cell from a pool of candidate molecules, comprising:

Applicant : Virginia W. Cornish
Serial No.: 10/705,644
Filed : November 10, 2003
Page 4

(a) covalently bonding each molecule in the pool of candidate molecules to a methotrexate moiety to form a screening molecule;

(b) introducing the screening molecule into a cell which expresses a first fusion protein comprising a binding domain capable of binding methotrexate, a second fusion protein comprising the known target, and a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein;

(c) permitting the screening molecule to bind to the first fusion protein and to the second fusion protein so as to activate the expression of the reporter gene;

(d) selecting which cell expresses the reporter gene; and

(e) identifying the small molecule that binds the known target.

148-149. (Canceled)

150. (Original) The method of claim 147, wherein the molecule is obtained from a combinatorial library.

151. (Original) The method of claim 147, wherein the steps (b)-(e) of the method are iteratively repeated in the presence of a preparation of random small molecules for competitive binding with the hybrid ligand so as to identify a molecule capable of competitively binding the known target.

152. (Original) The method of claim 147, wherein the first fusion protein or the second fusion protein is DHFR- (DNA-binding domain).

153. (Original) The method of claim 147, wherein the first fusion protein or the second fusion protein is DHFR-LexA.

Applicant : Virginia W. Cornish
Serial No.: 10/705,644
Filed : November 10, 2003
Page 5

154. (Original) The method of claim 147, wherein the first fusion protein or the second fusion protein is DHFR-(transcription activation domain).

155. (Original) The method of claim 147, wherein the first fusion protein or the second fusion protein is DHFR-B42.

156. (Original) The method of claim 147, where the cell is a yeast cell, a bacteria cell or a mammalian cell.

157. (Original) The method of claim 147, where the cell is *S. cerevisiae* or *E. coli*.

158. (New) A method for identifying a protein target to which a molecule is capable of binding, comprising:

(a) providing a screening molecule comprising a methotrexate moiety or an analog of methotrexate covalently bonded to a ligand which has a specificity for an unknown protein target;

(b) introducing the screening molecule into a cell which expresses a first fusion protein comprising a binding domain capable of binding methotrexate, a second fusion protein comprising the unknown protein target, and a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein;

(c) permitting the screening molecule to bind to the first fusion protein and to the second fusion protein so as to activate the expression of the reporter gene;

(d) selecting which cell expresses the reporter gene; and
(e) identifying the unknown protein target.

159. (New) The method of claim 158, wherein the unknown protein target is encoded by a DNA from the group consisting of genomicDNA, cDNA and syntheticDNA.

Applicant : Virginia W. Cornish
Serial No.: 10/705,644
Filed : November 10, 2003
Page 6

160. (New) The method of claim 158, wherein the ligand has a known biological function.